PATENT COOPERATION TREATY

IPD

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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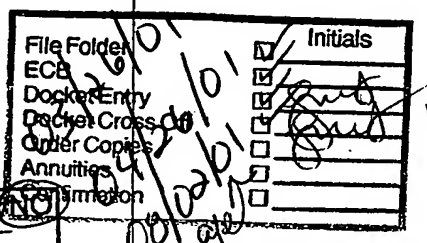

Subject to PTA? ~~YES~~ NO
per docket/~~ECB~~
mm 02/01/01

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	26.01.2001
Applicant's or agent's file reference: B0801/7169WO	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/08586	31/03/2000	02/04/1999

International Patent Classification (IPC) or both national classification and IPC

A61K31/7088

Applicant

THE BRIGHAM AND WOMEN'S HOSPITAL, INC.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☒	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 02/08/2001.

Name and mailing address of the international preliminary examining authority:

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Authorized officer / Examiner
Peris Antoli, B

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I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-51	as originally filed				

Claims, No.:

1-146	as originally filed				

Drawings, sheets:

1/10-7/10,9/10, 10/10	as originally filed				
8/10	as received on	21/06/2000	with letter of	19/06/2000	

Sequence listing part of the description, pages:

46, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-64, 67-110, 114-115, 118, 122, 125, 127-137, 139, 144-145 (all completely); 111-113, 116-117, 119-121, 123-124, 126, 138, 140-143, 146 (all partially); 65-66, 111-113, 116-117, 119-121, 123-124, 126, 138, 140-143, 146 (industrial applicability),

because:

☒ the said international application, or the said claims Nos. 65-66, 111-113, 116-117, 119-121, 123-124, 126, 138, 140-143, 146 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-64, 67-110, 114-115, 118, 122, 125, 127-137, 139, 144-145 (all completely); 1-64, 67-110, 114-115, 118, 122, 125, 127-137, 139, 144-145 (all completely); 111-113, 116-117, 119-121, 123-124, 126, 138, 140-143, 146 (all partially).

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:
see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	65
Inventive step (IS)	Claims	65-66
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II
Priority

1. This opinion is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document Tzianabos, A. et al.: ABSTRACTS OF THE 99 TH GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, CHICAGO, US, MAY 30-JUNE 3, 1999, vol. 99, - 3 June 1999 (1999-06-03) pages 37-38, WASHINGTON, US, cited in the international search report could become relevant to assess whether the claimed subject matter satisfies the criteria set forth in Article 33(1) PCT.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2. As indicated in the international search report (see Form PCT/ISA/210 Box. I.2), the search of the present claims 1-64 and 67-146 has been limited to those parts relating to the compounds specified in examples 2-9 and 12-14; i.e. *Bacteroides fragilis* capsular polysaccharide A (PS A), *Streptococcus pneumonia* type 1 capsular polysaccharide (CP) and $(K\text{-}D)_n$ peptides.

2.1 *B. fragilis* PS A and *S. pneumonia* type 1 CP have a molecular weight greater than 50 kilodaltons (see description: p. 15, l. 24-25, wherein it is indicated that *B. fragilis* PS A is composed of approx. 200 tetrasaccharide units - which will result in a molecular weight of approx. 165 kDa; and p. 50, l. 8-10 wherein it is indicated that *S. pneumonia* type 1 CP has a molecular weight of 80 kDa). Said polymeric polysaccharides do therefore not fall within the scope of polymers defined in the present independent claims 1, 19, 37, 61, 63, 67, 101, 103, 104, 106 and 108 and 127. The same applies to the dependent claims 2-18, 20-36, 38-60, 62, 64, 68-100, 102, 105, 107, 109-110 and 128-137. Furthermore, the referred polysaccharides do not fall within the scope of the polymers covered by the present dependent claims 114-115, 118, 122, 125, 139, 144 and 145.

2.2 The $(K\text{-}D)_{1\text{-}25}$ peptides disclosed in examples 4-5 of the present application consist of repeating units having a charge motif composed of positively charged free amino moiety and a negative charge. The positive charge of the repeating units (or charge motifs) are separated only by one negatively charged amino acid, namely glutamic acid (D). It is hence apparent that the distance between the positive charges in two consecutive repeating units will be less that 32Å. The referred K-D peptides do therefore not fall within the scope of polymers defined the present independent claims 1, 19, 37, 61, 63, 67, 101, 103, 104, 106, 108, 111, 127 and 138. The same applies to the dependent claims 2-18, 20-36, 38-60, 62, 64, 68-100, 102, 105, 107, 109-110, 112-126, 128-137 and 139-146.

2.3 According to Rule 66.1(e) PCT, no international preliminary examination will be carried out in respect of the subject matter which is not covered by the search report.
Hence no opinion will be given regard to novelty, inventive step and industrial applicability of the present claims 1-64, 67-110, 114-115, 118, 122, 125, 127-137, 139, 144 and 145.

2.4 Concerning claims 111-113, 116-117, 119-121, 123-124, 126, 138, 140-143 and 146, only a partial opinion will be given; namely, as far as said claims encompass the polysaccharides *B. fragilis* PS A and *S. pneumonia* type 1 CP.

3. Claims 65-66, 111-113, 116-117, 119-121, 123-124, 126, 138, 140-143 and 146 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV
Lack of unity of invention

4. Reference is made to the following documents:

D1: V.K. PERUMAL ET AL.: 'PROTECTIVE EFFECT OF INTERLEUKIN-2 ON EXPERIMENTAL INTRA-ABDOMINAL ABSCESS DEVELOPMENT DUE TO

BACTEROIDES FRAGILIS.' CLINICAL RESEARCH, vol. 38, no. 2, 1990, page 550A XP000952900 NEW YORK, N.Y., US

D2: DE 37 04 389 A (BLUTSPENDEDIENST DT ROTE KREUZ) 25 August 1988 (1988-08-25)

D3: WO 96 07427 A (BRIGHAM AND WOMEN'S HOSPITAL, INC.) 14 March 1996 (1996-03-14) cited in the application

D4: W.M. KALKA-MOLL ET AL.: 'BACTEROIDES FRAGILIS NCTC 9343 CAPSULAR POLYSACCHARIDE PS A AND THE EFFECT OF CHAIN LENGHT ON T CELL PROLIFERATION.' ABSTRACTS OF THE 98 TH GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, ATLANTA, US, MAY 17-21, 1998, vol. 98, 1998, page 123 XP002150693 WASHINGTON, US

5. The international preliminary examining authority is of the opinion that the present application does not comply with the requirements of unity of invention as set forth in the PCT regulations (Rule 13.1 PCT) because it relates to the following inventions or groups of inventions which are not so linked as to form a single general inventive concept (Rule 13.1 PCT):

(1) Compositions comprising a polymer as defined in the present claim 1 (except for the limitation concerning the neutral character of the intervening sequence) or a polypeptide as defined in the present claim 19. **[Claims 1-36]**.
Use of said polymers and/or polypeptides for (i) inducing IL-2 secretion or treating IL-2-responsive disorders, (ii) protecting against abscess formation, (iii) activating T-cells or treating T-cell-responsive disorders, (iv) treating disorders characterized by inappropriate IgG antibody response to specific antigens; (v) reducing postoperative surgical adhesions. **[Claims 36-64 and 67-110]**.
Use of zwitterionic polymers as defined in the present claim 111, excluding the aforementioned polymers and polypeptides, for reducing postoperative surgical adhesions. **[Claims 111-146]**.

(2) Method for inducing protection against abscess formation using IL-2 or an IL-2 inducing compound other than those mentioned in invention (1) above.

5.1 It is a priori apparent that the aforementioned groups of inventions (1) and (2) are not linked single general inventive concept; i.e. a single compound (or type of compounds) or a single particular use.

Even if a common concept could be seen in the use of IL-2 or an IL-2 inducing compound for protecting against abscess formation, it is to be noted that said concept is not novel and not inventive, because the use of IL-2 for protecting against abscess formation is already known from D1, and compounds that induce IL-2 are also already known (see e.g. D2: p. 2, l. 32-34, 46 in conjunction with p. 3, l. 19-22; and p. 4, table 1).

6. According to Rule 68.1 PCT, the international preliminary examining authority has chosen not to invite the applicant to restrict the claims or to pay additional fees.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

7. Claims 65-66 do not meet the requirements of Art. 33(2) and/or 33(3) PCT for the following reasons:

7.1 As indicated in item 5.1 above, D1 discloses the use of IL-2 for protecting against abscess formation.

7.1 D1 does therefore destroy the novelty of the subject matter of the present claim 65.

7.2 D1 also destroys the inventive step of the subject matter of claims 65-66, because in the light of said document, it would had been obvious to the skilled person to use compounds that induce IL-2 for protecting against abscess formation. [Note that as also indicated item 5.1, compounds that induce IL-2 are also known from the state of the art; e.g. from D2].

8. None of the prior art documents cited in the search report discloses or suggests the use of *B. fragilis* PS A and *S. pneumonia* type 1 CP for reducing postoperative

surgical adhesions.

8.1 Thus, as far as claims 111-113, 116-117, 119-121, 123-124, 126, 138, 140-143 and 146 relate to the aforementioned use of *B. fragilis* PS A and *S. pneumonia* type 1 CP, the subject matter of said claims is considered new and inventive over the cited prior art. Said claims do therefore meet the requirements of Art. 33(2) and 33(3) PCT.

9. For the assessment of the present claims 65-66, 111-113, 116-117, 119-121, 123-124, 126, 138, 140-143 and 146 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

10. Despite the fact that no opinion can be given regard to novelty, inventive step and industrial applicability of the present claims 1-64, 67-110, 114-115, 118, 122, 125, 127-137, 139, 144 and 145 because they have not been searched (see items 2 and 2.3 above), the following is to be noted for the sake of completeness:

10.1 D3 (see e.g. summary of the invention on pp. 3-5; and p. 7) discloses that polymers having a particular structural motif that includes a positively charged free amino group and a negatively charged group on a repeating unit are capable of inducing "cross-protection" against abscess formation by a variety of bacteria, and that said protective effect is mediated by T-cells. The polymers typically comprise repeating units of a charge motif characteristic of *B. fragilis* PS A. Preferably the polymer capsular is *isolated B. fragilis* PS A , although other naturally occurring polysaccharides can be modified to produce polymers having the aforementioned particular structural motif. As indicated in D3 (see p. 8, l. 9-10), the molecular weight of the polymers may vary from 0.5 to 20.000 kDa.

Thus, D3 anticipates the subject matter of the present claims 1-18, 67-100 and 103, as far as they cover polymeric compounds having the repeating structural

charge motif disclosed in D3 and the use of said compounds for protecting against abscess formation and for activating T-cells.

10.2 D4 discloses the ability of *B. fragilis* PS A and small fractions thereof (with a molecular weight of 17 to 78 kDa) to stimulate T-cell proliferation.

Thus, D4 appears to anticipate the subject matter of the present claims 1-18 and 103, as far as they cover compounds disclosed in D4 and related ones.

Re Item VIII
Certain observations on the international application

11. Claims 1-64 and 67-146 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the technical contents of application. The particular effects of certain compounds shown in experimental examples of the application do not provide basis for generalization of said effects to all given compounds falling within the definitions given in the independent claims 1, 19, 37, 63 or 111.